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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/866,248	05/25/2001	Christophe P.G. Gerald	1795/57155-AA JPW/BJA	6169

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EXAMINER	
MURPHY, JOSEPH F	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 10/06/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/866,248	GERALD ET AL.	
	Examiner	Art Unit	
	Joseph F Murphy	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *76,77,97,98,107,108,134,135,142-145,158,161 and 183-191* is/are pending in the application.

4a) Of the above claim(s) *76,77,97,98,107,108,134,135,142-145,158161* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *183-191* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Formal Matters

Claims 178-180 were cancelled, and new claims 185-191 were added in Paper No. 11, 7/11/2003. Claims 76-77, 97-98, 107-108, 134-135, 142-145, 158, 161, 183-191 are pending.

Election/Restrictions

Applicant's election with traverse of Group II, which reads on claims 183-191 in Paper No. 11, 7/11/2003 is acknowledged. The traversal is on the ground(s) that the Groups are not independent and distinct, and that a search of the two Groups could be made without imposing an undue burden on the Examiner. This is not found persuasive for the following reasons.

Applicant's attention is directed to MPEP 808.02 which states that "Where the related inventions as claimed are shown to be distinct under the criteria of MPEP 806.05 (c-i), the examiner, in order to establish reasons for insisting upon restriction, must show by appropriate explanation one of the following: (A) Separate classification thereof; (B) A separate status in the art when they are classifiable together; (C) A different field of search." As set forth in the Restriction requirement of Paper No.7, 12/17/2002, Group I is classified in class 435, subclass 7.2; Group II is classified in class 435, subclass 69.6. The separate classification established for each Group demonstrates that each distinct Group has attained recognition in the art as a separate subject for inventive effort, and also a separate field of search, thus imposing a search burden on the Examiner. Thus, the Restriction requirement is proper.

The requirement is still deemed proper and is therefore made FINAL. Claims 76-77, 97-98, 107-108, 134-135, 142-145, 158, 161 are withdrawn from consideration pursuant to 37 CFR 1.142(b). Claims 183-191 are under consideration.

Claim Rejections - 35 USC § 112 first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 183-191 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method of preparation of a pharmaceutical composition which is an agonist of a mammalian NPFF receptor. This method is not enabled because i) the specification is not enabled for the full scope of mammalian NPFFF receptors; ii) the specification is not enabled for a method of preparing a pharmaceutical composition because the specification does not teach how to make an agonist of NPFF receptor; iii) the specification is not enabled for a method of preparing a pharmaceutical composition because the specification does not teach the nexus between the agonist and any disease state.

Firstly, claims 183-191 are overly broad in the recitation of "mammalian" NPFF receptor. Insufficient guidance is provided in the specification as to how one of ordinary skill in the art would generate polynucleotides encoding polypeptides from all mammals, that would exhibit the same biological function as the human NPFF receptor polypeptide exemplified in the specification. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. Applicant has only taught SEQ ID NO: 4 and 8. Applicant has provided little or no

guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. Applicants do not disclose any actual or prophetic examples on expected performance parameters of any of the possible variants of NPFF.

It is known in the art that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function. For example, Voet et al. (1990) teaches that a single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph). It is also known in the art that a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. Thus, the amino acid sequence of a polypeptide determines

its structural and functional properties, and predictability of which amino acids can be substituted is extremely complex and well outside the realm of routine experimentation, because accurate predictions of a polypeptide's structure from mere sequence data are limited. Since detailed information regarding the structural and functional requirements of the encoded proteins are lacking, it is unpredictable as to which encoding variations, if any, meet the limitations of the claims.

Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Secondly, the specification is not enabled for a method of preparing a pharmaceutical composition because the specification does not teach how to make an agonist of NPFF receptor, but only how to screen for an agonist of the NPFF receptor. It would require undue experimentation for one of skill in the art to practice the claimed method, since the skilled artisan would have to first generate potential agonists of NPFF receptor, then test for activity. Because the structure of an agonist determines its functional properties, and predictability of the function based on the structure is extremely complex, accurate predictions of an agonist's function from structural data are limited. Thus, since Applicant has only taught how to test for agonists of

NPFF receptor, but has not taught how to make agonists of NPFF receptor it would require undue experimentation of one of skill in the art to practice the claimed method of preparation of an agonist.

Thirdly, the specification is not enabled for a method of preparing a pharmaceutical composition because the specification does not teach the nexus between the agonist and any disease state. Neither the specification nor any art of record teaches a relationship to any specific disease or establish any involvement of the NPFF receptor polypeptide in the etiology of any specific disease or teach how to use the polypeptides of the instant claim as a diagnostic. Lacking this information, one of skill in the art would need to determine the role of the NPFF receptor protein in a disease state, then determine whether an NPFF receptor agonist would treat the disease state. It would require one of skill in the art to determine the nexus between the disclosed polypeptide and all diseases, since the claims as written encompass the agonist of the instant claims as a treatment for any and all diseases, since no disease or condition is set forth as a limitation. This would require undue experimentation on the part of the skilled artisan, since it would require determining the cause of all diseases, and the correlation between the NPFF receptor agonist and all diseases.

Claims 183-191 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The claims are drawn to a method of preparation of a pharmaceutical composition which is an agonist of a mammalian NPFF receptor. This method is not described because i) the specification does not describe the full scope of mammalian NPFF receptors; ii) the specification does not describe a method of preparing a pharmaceutical composition because the specification does not describe an agonist of NPFF receptor.

Claims 183-191 are drawn to methods of preparing a pharmaceutical composition of an agonist to mammalian NPFF receptors. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the genus of polypeptides used in the claimed method. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. There is no description of

the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Structural features that could distinguish the compounds in the genus from other seven transmembrane region compounds are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polypeptides encompassed: there is no guidance in the art as to what the defining characteristics of the polypeptides might be. Thus, no identifying characteristics or properties of the instant mammalian NPFF receptor polypeptides are provided such that one of skill would be able to predictably identify the molecules which would function in the claimed method.

Additionally, the specification does not describe a method of preparing a pharmaceutical composition because the specification does not provide written description of an agonist of NPFF receptor, but only how to screen for an agonist of the NPFF receptor. However, an assay for finding a product is not a description of the agonist. Since no structural or specific functional characteristics of an NPFF agonist are provided, one of skill in the art would conclude that Applicant was not in possession of the agonist.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 184, 186 and 187 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 184 is vague and indefinite in the recitation of the term "agonist" in the last line of subsection (a), because in the preamble the process is directed to preparing an antagonist of NPFF receptor. Thus the metes and bounds of the claim cannot be determined.

Claims 186 and 187 are vague and indefinite because the claims need to more clearly distinguish between the compounds. For example, in claim 186 (b) it is not clear which compound is to be recovered, the first or the second as described in subsection (a). Furthermore, in claim 187 (b) it is not clear which of the plurality of compounds is to be considered 'the" compound, nor is it clear whether the plurality contains compounds which are known to bind NPFF, or a separate compound is known to bind. This rejection could be obviated by more clearly labeling the known ligands from the test compounds, and clearly setting forth which are to recovered and made into a pharmaceutical composition.

Conclusion

No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph F. Murphy whose telephone number is 703-305-7245. The examiner can normally be reached on M-F 7:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on 703-308-6564. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-0294 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Joseph F. Murphy, Ph. D.
Patent Examiner
Art Unit 1646
October 2, 2003

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